DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group I, claims 1-7 in the reply filed on 7/11/08 is acknowledged. The election of SEQ ID NO:7 as the species of antigenic determinant is further acknowledged. The traversal is on the ground(s) that the claims encompass a special technical feature which does define a contribution over the prior art of Carey et al. (Reply, page 3).

This is not found persuasive because a mere broad allegation that the restriction requirement is in error does not comply with the requirements of 37 CFR § 1.111. Under this rule, Applicant is required to specifically point out the reasons on which he or she bases his or her conclusions that a requirement to restrict is in error. See MPEP § 818.03(a). In the instant case, while a special technical feature is broadly alleged, Applicant has not particularly pointed out or identified what this feature is. For reasons of record, it is maintained that the unity of invention is lacking because the technical feature linking the claimed inventions does not represent a contribution over the prior art.

Applicant further argues that it would appear that a search for the inventions would significantly overlap, such that there would not appear to be s a serious burden in examining all Groups (Reply, page 3).

This is not found persuasive because Applicant is referring to the requirement to demonstrate search burden that pertains to applications filed under 35 U.S.C. 111(a) (see MPEP 801). There is no corresponding requirement to demonstrate search burden in applications filed under 35 U.S.C. 371.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 8-13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/11/08 as discussed above.

Priority

3. The present application is a proper National Stage (371) entry of PCT Application No. PCT/JP03/08123, filed 06/26/2003. Acknowledgment is also made of Applicant's claim to priority under 35 U.S.C. 119(a)-(d) to Application No. 2002-187479, filed on 06/27/2002 in Japan.

Information Disclosure Statement

4. Applicant's Information Disclosure Statements filed 8/15/05 and 7/19/07 have been received and entered into the application. The references therein have been considered by the examiner as indicated on the attached form PTO-1449.

5. Cite No. 13 on the IDS of 8/15/05 (Robertson et al.) has been lined through to avoid duplicate citation, as the publication was previously listed on the IDS as Cite No. 8. The reference has been considered by the Examiner.

6. Applicant is reminded that the listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Specification

7. The disclosure is objected to because of the following informalities:

8. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See page 3, second paragraph. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

9. The brief description of Figure 10 on page 8 of the specification refers to "the amino acids sequence shown in SEQ ID NO:1". However, the sequence listing filed on 12/27/2004 indicates that SEQ ID NO:1 is a 550-amino acid protein, while the sequence depicted in Figure 1 is not that of a 550-amino acid protein.

Appropriate correction and/or clarification are required.

Claim Objections

10. Claim 3 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 3 recites that "a protein consisting of the N-terminal fragment of Cochlin" is detected, which fails to further limit the recitation in claim 1 that Cochlin *per se* is detected. The instant specification defines Cochlin as "a protein encoded by a COCH gene" (page 9). However,

the claim terminology "a protein consisting of the N-terminal fragment of Cochlin" would encompass (for example) proteins generated by recombinant engineering techniques and would not necessarily encoded or expressed by a COCH gene. Therefore, the claim broadens, rather than further limits, the scope of the independent claim.

This objection may be obviated by reciting that the method detects "a --Cochlin-- protein consisting of…".

Claim Rejections - 35 USC § 112

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

13. Claims 1 and 3-7 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: a step in which a perilymph fistula is detected.

The preamble of claim 1 recites a method "for detecting a perilymph fistula", but the claim concludes with the step of detecting the existence of Cochlin. As such, the claims are incomplete because they recite neither an active method step in which a perilymph fistula is detected nor a correlation step describing how the results of the assay accomplish the objective of the method as stated in the preamble.

14. Claim 3 recites the limitation "the N-terminal fragment of Cochlin" in line 3. There is insufficient antecedent basis for this limitation in the claim. In addition, the scope of the claim is unclear because an "N-terminal fragment" might refer to the N-terminal amino acid of a protein, to the N-terminal half of the protein, or to various N-terminal portions thereof. As such, the reference to an "N-terminal fragment" is ambiguous because no specific or limiting definition for this term has been provided in the instant specification. Furthermore, different researchers may define domain boundaries differently. For all of these reasons, the metes and bounds of the claim are unclear because it is not apparent what portion or portions of Cochlin would be considered to represent "the N-terminal fragment".

15. Claim 6 recites an antibody that recognizes an antigenic determinant contained in an amino acid sequence portion "corresponding to" amino acids at positions 36-127 of the amino acid sequence shown in SEQ ID NO:1. The terminology "corresponding to" is vague and indefinite. The specification does not specifically define what amino acids "corresponding to" would encompass, or provide a standard for understanding the scope of this term. For example, what level(s) of correspondence would be encompassed and in what way could the amino acids differ from those at positions 36-127 of SEQ ID NO:1 and still be considered to correspond? For all of these reasons, the metes and bounds of the claim are unclear.

Claim Rejections - 35 USC § 103

16. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

> having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikezano et al. (Biochimica et Biophysica Acta 1535 (2001) 258-265) in view of the Dictionary of Medicine, definition for the term "perilymph" (2000); Peter Collin Publishing, London: Peter Collin Publishing. Retrieved October 21, 2008, from http://www.credoreference.com/entry/1051726/), Magal et al. (US 6,274,554 B1), Wall et al. ("Perilymph fistula pathophysiology" Otolaryngol Head Neck Surg. 1995 Jan;112(1):145-53), and Botstein et al. (US 6,913,919 B2).

Izekano et al. teach a method for detecting the protein product of the *Coch* gene (i.e., Cochlin) in homogenized inner ear tissue samples (see in particular the abstract; page 259, section 2.1; and page 264, right column, penultimate paragraph).

The reference differs from the claimed invention in that it fails to specifically teach detection of Cochlin in a body fluid existing in the middle ear.

The Examiner finds the following facts:

The Dictionary of Medicine teaches that perilymph was fluid known to exist in the labyrinth of the inner ear.

Magal et al. discusses physiology of the inner ear and teaches that proteins penetrate the membrane of the round window into the perilymph of the inner ear (column 20, lines 45-48).

Wall et al. relates to the pathophysiology of perilymph fistula, which is an abnormal communication between the inner and middle ear cavities that results in leakage of perilymph from the inner ear into the middle ear (page 145, abstract and left column). The reference teaches that diagnostic methods are emerging for the detection of perilymph fistula, based on detection of a marker that has passed from the inner ear space (where perilymph is normally found) to the middle ear space (page 147, paragraph bridging the left and right columns; and page 148, paragraph bridging left and right columns). Such perilymph markers can be endogenous substances that are unique to perilymph or cerebrospinal fluid but absent in serum (page 149, "Perilymph Markers"). In other words, proteins that are specific to perilymph can be used as markers to detect leakage of perilymph into the middle ear. Wall et al. teach that such markers include β2-Transferrin, which can be detected by gel-electrophoresis and immunoblotting (abstract and page 149).

Botstein et al. teaches that Cochlin (Coch-B2) is specifically expressed in the inner ear. See column 12, line 60 to column 13, line 10.

From the teachings of The Dictionary of Medicine that the labyrinth of the inner contains perilymph, there is a strong basis to believe that the inner ear tissue samples studied by Izekano et al. contained perilymph, as these tissue samples included the inner ear labyrinths (see Izekano et al. page 264, right column, penultimate paragraph).

Furthermore, although Izekano et al. detected Cochlin in the homogenized tissue samples and did not separately analyze the perilymph component therein for the presence of Cochlin, one

of ordinary skill in the art would reasonably expect this protein to be found in perilymph because Magal et al. taught that proteins penetrate into the perilymph. As an inner ear protein, one of ordinary skill in the art would reasonably expect Cochlin to exist in perilymph.

Therefore, from the teachings of Izekano et al., the Dictionary of Medicine, and Magal et al., it would have been obvious to one of ordinary skill in the art to conclude that the protein Cochlin is found in perilymph.

In addition, in view of the teachings of Wall et al. and Botstein et al., it would have been further obvious to one of ordinary skill in the art to detect Cochlin as a perilymph marker in fluid in the middle ear. One would have been motivated to do this in order to detect perilymph fistula. In particular, Wall et al. taught that endogenous substances that are found in perilymph but absent in serum can be used as perilymph markers in order to detect perilymph fistula (i.e., leakage of perilymph from the inner to the middle ear). Botstein et al. teaches that Cochlin was known to be specific to the inner ear. Consequently, one of ordinary skill in the art would reasonably expect Cochlin not only to be expressed in perilymph as discussed above, but also to be specific to the inner ear and not also expressed in serum, for example.

In summary, it would have been obvious to one of ordinary skill in the art to recognize Cochlin as a specific perilymph marker according to the criteria taught by Wall et al., and to detect this protein in middle ear fluid in order to detect perilymph fistula (as taught by Wall et al.).

With respect to claim 3, Izekano et al. teach that Cochlin exists in the inner ear as different isoforms, identified as p63, p44, and p40. p63 is the most amino terminal portion of Cochlin (see page 264, left column; and also Tables 1-3 and Figure 4). Therefore, because

multiple Cochlin isoforms were known in the art to exist in the inner ear, including the N-terminal Cochlin fragment p63, it would have been further obvious to detect this isoform of Cochlin when analyzing middle ear fluid for the presence of Cochlin. The selection of one of a finite number of known isoforms would have been obvious.

With respect to claim 4, Wall et al. teaches detection of the perilymph marker β2-Transferrin by gel-electrophoresis and immunoblotting (abstract and page 149). Given that such methods were known in the art to be suitable for detecting perilymph markers, it would have been obvious to select such known immunological methods detect Cochlin as a perilymph marker.

19. Claims 4-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ikezano et al. in view of the Dictionary of Medicine, Magal et al., Wall et al., and Botstein et al. as applied to claim 1 above, and further in view of Robertson et al. (Human Molecular Genetics 2001, Vol. 10, page 2493-2500), the Academic Press Dictionary of Science and Technology (definition for the term "polyclonal"; Oxford: Elsevier Science & Technology (1996); retrieved October 22, 2008, from http://www.credoreference.com/entry/3144515/) and Wolfe, S.L., (Molecular and Cellular Biology, 1993, pages 790-793).

The references are as discussed above, which teach methods for detecting Cochlin substantially as claimed. Izekano et al. teaches p63, a N-terminal fragment of Cochlin. Wall et al. teaches immunoblotting procedures to detect perilymph markers. However, the references fail to specifically teach detecting of Cochlin using an anti-Cochlin N-terminal fragment antibody.

Robertson et al. teach methods for detecting the human protein cochlin using a polyclonal antibody raised against the N-terminal 135 residues of cochlin (abstract and pages 2495 and 2498-2499, the sections entitled "Generation of antibody against cochlin").

It would have been obvious to employ the anti-Cochlin N-terminal fragment antibody of Robertson et al. to detect Cochlin in middle ear fluid as a marker of perilymph fistula in the method of Ikezano et al., the Dictionary of Medicine, Magal et al., Wall et al., and Botstein et al. because the selection of a known material for its known purpose would have been obvious. One would have had a reasonable expectation of success because Robertson et al. taught that the antibody successfully detected Cochlin in biological samples.

With respect to claim 6, the polyclonal antibody of Robertson et al. was raised against a peptide sequence corresponding to amino acid residues 27-161 of human cochlin (see Figure 1B and legend). The Examiner notes that SEQ ID NO:1 is the amino acid sequence of human cochlin as disclosed instantly. Although Robertson et al. teach an antibody that recognizes an epitope within residues 27-161, and do not specifically mention residues 36-127, the reference nonetheless reads on the claim for the following reasons.

First, the claim terminology "an antigenic determinant contained in an amino acid sequence portion corresponding to amino acids at positions 36 to 127 of the amino acid sequence shown in SEQ ID NO:1" may be interpreted broadly, as the specification does not specifically indicate what a sequence "corresponding to" another sequence might encompass (see rejection under § 112, 2nd paragraph above). Therefore, amino acids 27-161 of human cochlin may be said to "correspond to" amino acids 36-127 in that these are overlapping stretches of the same protein.

When the claim is given its broadest reasonable interpretation, therefore, the teachings of Robertson et al. read on the recited antibody.

Second, it was well known in the art that polyclonal sera comprises a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen. See the Academic Press Dictionary of Science and Technology, which defines a polyclonal antibody as a population of heterogeneous antibodies derived from multiple clones, each of which is specific for one of a number of determinants found on an antigen.

In addition, Wolfe discloses that the size of an epitope (i.e., antigenic determinant) bound by an antibody is between 3 to 16 amino acids in length (see particularly the bottom of the left column of page 791). As such, there is a strong scientific basis to believe that the polyclonal antibody directed against amino acids 27-161 of human cochlin would necessarily recognize antigenic determinant within amino acids 36-127 of this protein, given that these two sequences share numerous antigenic determinants.

With respect to claim 7, the Examiner notes that the claims employ open transitional language ("having"). In other words, the antibody recognizes an antigenic determinant found in a polypeptide that includes the amino acid sequence of SEQ ID NO:7, but the polypeptide may include additional amino acid residues on either end of SEQ ID NO:7. The claims therefore read on an antibody that recognizes an epitope found within the full-length Cochlin protein, for example.

The antibody of Robertson et al. was raised against a peptide sequence corresponding to amino acid residues 27-161 of human cochlin (see Figure 1B and legend). As disclosed instantly, SEQ ID NO:7 corresponds to amino acid residues 114-127 of human cochlin. Therefore, in

teaching an antibody that recognizes an epitope within amino acid residues 27-161 of human cochlin, the reference reads on an antibody that recognizes an epitope within a protein that includes amino acid residues 114-127 of cochlin (i.e., SEQ ID NO:7).

In addition, because the polyclonal antibody of Robertson et al. includes a mixture of antibodies of different specificities directed toward multiple antigenic determinants present on a particular antigen, there is a strong scientific basis to believe that the antibody would necessarily recognize epitopes contained within amino acids 114-127 of cochlin, given that this sequence shares numerous epitopes in common with the larger sequence defined by residues 27-161.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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